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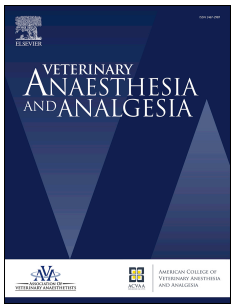

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Cardiac troponin I in dogs anaesthetized with propofol and sevoflurane: the influence of medetomidine premedication and inspired oxygen fraction

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Abstract

Objective To investigate changes in serum cardiac troponin I (cTnI) concentrations in dogs in which medetomidine was used for sedation or for premedication prior to anaesthesia with propofol and sevoflurane.

Study design Prospective clinical study.

Animals A total of 66 client-owned dogs.

Methods The dogs were sedated with medetomidine (0.04 mg kg^{-1}) intravenously (IV) (group M; n = 20) and left to breath room air or anaesthetized with propofol (6.5 ± 0.76 mg kg^{-1} IV) and sevoflurane (4.5% vaporizer setting) in oxygen (group P+S; n = 20) or with medetomidine (0.04 mg kg^{-1} IV), propofol (1.92 ± 0.63 mg kg^{-1}) and sevoflurane (3% vaporizer setting) in oxygen (group M+P+S; n = 26), respectively. After 35 minutes, medetomidine was antagonized with atipamezole (0.1 mg kg^{-1} intramuscularly). Blood samples for serum cTnI determination were taken before sedation or anaesthesia, 6 and 12 hours and 4 days thereafter. Serum cTnI concentrations were measured with the Architect STAT Troponin-I assay.

Results Before sedation or anaesthesia, cTnI concentrations were above the detection limit in 22 out of 66 (33%) of dogs. Compared to basal values, cTnI concentrations significantly increased at 6 and 12 hours in all groups and at day 4 in group M. There were no differences in cTnI concentration between groups at baseline, at 6 hours and at 4 days. At 12 hours, cTnI concentrations were significantly higher in groups M and P+S, respectively, compared to group M+P+S.

Conclusions and clinical relevance Oxygenation during anaesthesia and reduction of propofol and sevoflurane dose due to the sparing effects of medetomidine might have

played a role in alleviation of myocardial hypoxic injury as indicated by the less severe and short-lived increase of cTnI in the M+P+S group.

Keywords cardiac troponin I, dogs, medetomidine, propofol, sevoflurane

Introduction

Cardiac troponin I (cTnI), an inhibitory subunit of troponin, is a highly sensitive and specific marker of myocardial cell injury in dogs (Burgener et al. 2006). In healthy dogs cTnI is present at low concentrations in the blood and provides information about cardiac-specific injury (Sleeper et al. 2001; Winter et al. 2014; Winter et al. 2017). During surgery under general anaesthesia, subclinical myocardial damage and leakage of cTnI from myocytes may occur in dogs (Pelander et al. 2008; Cilli et al. 2010; Verbiest et al. 2013). The relative effect of surgery and general anaesthesia on cTnI leakage from myocytes is still not known. To exclude the possible influence of surgical trauma, we investigated the effect of anaesthetic drugs on serum TnI concentration in dogs sedated for radiographic examination or anaesthetized for gastroscopy.

The effect of anaesthesia with propofol and sevoflurane with or without premedication with medetomidine on serum cTnI concentration in dogs has not yet been reported. Premedication with medetomidine decreases the anaesthetic requirements of propofol (Vainio 1991; Cullen & Reynoldson 1993; Lagerweij et al. 1993; Sap & Hellebrekers 1993; Hammond & England 1994; Thurmon et al. 1994). Dexmedetomidine, the active enantiomer of the racemate medetomidine, causes a dose-dependent decrease in sevoflurane minimum alveolar concentration in dogs (Moran-Muñoz et al. 2014; Hector

et al. 2017). We hypothesized that in dogs premedicated with medetomidine [administered intravenously (IV) at 0.04 mg kg^{-1}] and anaesthetized with propofol and sevoflurane, the increase in serum cTnI concentration would be less pronounced because of anaesthetic sparing effects in comparison to dogs anaesthetized with propofol and sevoflurane only.

However, it is not known whether medetomidine alone causes subclinical myocardial damage and resultant cTnI release into the bloodstream. Singletary et al. (2010) demonstrated that sedation with medetomidine and butorphanol does not cause a significant rise in serum cTnI concentration in dogs. They used medetomidine at a relatively low intravenous dose of 0.01 mg kg^{-1} and monitored cTnI concentration up to 24 hours after administration. The cardiovascular effects of medetomidine, bradycardia in particular, are dose related (Vainio & Palmu 1989; Cullen & Reynoldson 1993). We therefore investigated changes of serum cTnI concentrations in dogs in which medetomidine (0.04 mg kg^{-1} IV) was used for sedation or for premedication prior to anaesthesia with propofol and sevoflurane. None of the studies that investigated cTnI in dogs sedated with medetomidine (Singletary et al. 2010) or anaesthetized with various anaesthetic protocols (Saunders et al. 2009; Cilli et al. 2010; Verbiest et al. 2013) monitored serum cTnI concentration more than 24 hours after sedation or anaesthesia. Hence, in our study, serum concentration of cTnI was monitored at 6 hours, 12 hours and 4 days after basal measurements.

Materials and methods

Animals

Client-owned dogs of various breeds with no cardiac disease, as confirmed by echocardiography and electrocardiography examination, presenting for radiography as part of orthopaedic examination under sedation or general anaesthesia for gastroscopy were recruited for this study. All eligible dogs with informed owner consent that were presented between January and June 2015 were included. An *a priori* sample size calculation was not performed.

The study was approved by the Local Ethical Committee at University of Belgrade (Licence No. 01-19/11). Dogs were classified as 1 or 2 according to the American Society of Anesthesiologists' classification system. A pre-sedation complete blood count, white cell differential count and serum biochemistry profile including urea, creatinine, total protein, albumin, glucose, creatin kinase, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase (data not shown) were determined to exclude underlying diseases that might affect cTnI concentration.

Study protocol

A 22- or 20-gauge catheter was placed in the left or right cephalic vein. Dogs presenting for radiography (group M) were sedated with 0.04 mg kg^{-1} IV medetomidine (Domitor; Orion Pharma, Finland) and breathed room air during sedation. After 35 minutes, medetomidine was antagonized with 0.1 mg kg^{-1} atipamezol (Antisedan; Orion, Finland) administered intramuscularly (IM).

Dogs that presented for gastroscopy were randomly allocated (manual randomization with a toin coss) to either group P+S or group M+P+S. Dogs in group P+S were administered IV propofol (Diprivan; Astra Zeneca Ltd, UK) at 6 to 8 mg kg^{-1} to allow placement of an endotracheal tube. Anaesthesia was maintained with 4.5% sevoflurane

in oxygen (vaporizer setting, Sevorane; Abbott, Canada). Dogs in group M+P+S were premedicated with medetomidine (0.04 mg kg^{-1} IV), 2 minutes later 1 to 3 mg kg^{-1} IV propofol was administered to allow placement of an endotracheal tube. Anaesthesia was maintained with sevoflurane at 3% (vaporizer setting) in oxygen. A non-rebreathing (Mapleson F, body weight below 3 kg) or circle breathing system (body weight above 3 kg) were used as appropriate. All dogs were allowed to breathe spontaneously during anaesthesia. Duration of anaesthesia for gastroscopy was standardized to 35 minutes in both groups of dogs, and afterwards 0.1 mg kg^{-1} IM atipamezol was administered to group M+P+S.

The electrocardiogram, heart rate (HR), haemoglobin oxygen saturation (SpO_2) and non-invasive blood pressure were monitored with a monitor (Mindray PM-9000 Vet; Shanghai International Holding Corp. GmbH, Germany). Respiratory rate (f_R) was monitored by observation of chest movements in group M. Dogs undergoing general anaesthesia were additionally monitored with a capnograph and thermometer. Measurements of HR and mean arterial blood pressure (MAP) were recorded every five minutes during sedation or anaesthesia. For the purpose of statistical analysis measurements of both variables at 5, 15, 25 and 35 minutes were used. Hartmann's solution (Hemofarm AD, Serbia) was administered during sedation or anaesthesia at 5 mL kg^{-1} $hour^{-1}$.

Blood samples for determination of serum cTnI (basal values) were taken from the cephalic vein and collected into serum separator tubes (Vacuette; Greiner Bio-One, Austria) before medetomidine was administered (groups M and M+P+S) or before induction of anaesthesia with propofol (group P+S), 6 and 12 hours and 4 days thereafter. After coagulation and centrifugation (twice) at 3000g for 15 minutes using an

EBA-20 Hettich D-78532 centrifuge (Hettich GmbH & Co, Germany), serum samples were separated into aliquots and frozen at −70 °C until analysis. After thawing, the centrifugation procedure was repeated. Serum cTnI level was measured in singlicate using a commercial chemiluminescent microparticle immunoassay (CMIA) using an Architect i2000SR analyzer (Abbott Diagnostics, Germany). The analytical sensitivity of the ARCHITECT STAT Troponin-I assay was ≤ 0.01 ng mL^{-1}. The validation of the ARCHITECT STAT Troponin-I assay in our laboratory revealed intra- and inter-assay coefficients of variation between 1.5% and 4.6% for three levels of commercial controls. Values lower than the detection limit of 0.006 ng mL^{-1} were recorded as 0.0059 ng mL^{-1} for the purpose of statistical analysis.

Statistical analysis

Normal distribution of data was tested by the Shapiro-Wilk test. Differences between groups with detectable and undetectable concentration of serum cTnI regarding MAP and HR at basal values were compared using the Mann-Whitney Rank Sum test. Serum cTnI values at different sampling times were evaluated using the Friedman repeated measures analysis of variance on ranks. The Kruskal Wallis analysis of variance was used for comparison of serum cTnI concentrations, HR and MAP at all time points regarding different protocols. Differences with values of $p < 0.05$ were considered significant. SPSS for Windows ver. 22.0 (Armonk, NY: IBM Corp., USA) was used for all analyses. Data are presented as mean ± standard deviation.

Results

144 A total of 66 dogs completed the study of which 20 were sedated for radiography and
145 46 underwent general anaesthesia for gastroscopy. A total of 11 males and 9 females
146 weighing 17.2 ± 13.2 kg and aged 69.9 ± 32.9 months were included in group M; 11
147 males and 9 females weighing 10.7 ± 10.1 kg and aged 41.1 ± 25.2 months were
148 included in group P+S; and 10 males and 16 females weighing 19.4 ± 11.8 kg and aged
149 44.3 ± 25.1 months were included in group M+P+S. The dose of propofol administered
150 to achieve endotracheal intubation in group P+S and M+P+S was 6.5 ± 0.8 and 1.9 ±
151 0.6 mg kg^{-1}, respectively.
152 In group M, cTnI concentration was above the detection limit in nine out of 20 dogs
153 (45%) before sedation. Serum cTnI concentration increased 6 and 12 hours and 4 days
154 after sedation when compared to the basal values ($p = 0.007$, $p = 0.002$, and $p = 0.016$,
155 respectively) (Fig. 1). In group P+S, cTnI concentration was above the detection limit in
156 four out of 20 dogs (20%) before anaesthesia. An increase was observed at 6 and 12
157 hours after anaesthesia when compared to the basal values ($p = 0.035$ and $p < 0.001$,
158 respectively) (Fig. 2). In group M+P+S, cTnI concentration was above the detection
159 limit in nine out of 26 dogs (34.6%) before anaesthesia. There was an increase in cTnI
160 concentration at 6 and 12 hours after anesthesia when compared to basal values ($p <$
161 0.001) (Fig. 3).
162 Serum cTnI concentrations did not differ between groups at baseline as well as 6 hours
163 and 4 days after sedation or anaesthesia. At 12 hours, cTnI concentrations were lower in
164 group M+P+S when compared to group M ($p = 0.006$) and to group P+S ($p = 0.022$)
165 (Fig. 4).
166 There was no significant difference in HR between groups before sedation/anaesthesia.
167 A lower HR ($p < 0.001$) was observed during sedation/anaesthesia in groups M and

M+P+S when compared to group P+S (Table 1). There was no significant difference in MAP between groups before sedation/anaesthesia. A higher MAP ($p < 0.001$) was observed during sedation/anaesthesia in groups M and M+P+S compared to group P+S (Table 2).

Discussion

This study documents an increase of cTnI after medetomidine sedation or anaesthesia with propofol and sevoflurane with or without premedication with medetomidine in dogs presented for non-surgical interventions. Singletary et al. (2010) investigated the effect of IV medetomidine (0.01 mg kg^{-1}) combined with IV butorphanol (0.2 mg kg^{-1}) on serum cTnI concentrations in dogs. The dose of medetomidine used was four-times lower than that in this study. In the study of Singletary et al. (2010), serum cTnI concentrations were below the detection limit at all sampling times (6, 18 and 24-hours post-sedation) in all but three out of 20 dogs; two of the three dogs had serum cTnI concentrations above the detection limit at all sampling times, including prior to sedation. Singletary et al. (2010) used the Immulite assay (Immulite 2000 Immunoassay system; Siemens Healthcare Global) with an analytical sensitivity (minimum detectable concentration) of 0.2 ng mL^{-1} (O'Brien et al. 2006) for the determination of serum cTnI concentration. Saunders et al. (2009) and Cilli et al. (2010) also used an Immulite assay. Saunders et al (2009) reported that zero of 20 dogs had a preanaesthetic cTnI concentration above the detection limit and Cilli et al. (2010) reported that only 12 out of 105 (11.4%) dogs had preanesthetic cTnI concentrations above the detection limit.

191 The assay used in this study (ARCHITECT STAT Troponin-I) has a much higher
192 analytical sensitivity with a much lower detection limit of 0.006 ng mL^{-1}, which enables
193 more accurate determination of serum cTnI concentration. This is probably the reason
194 that in this study a higher number of dogs, 22 out of 66 (33%), had serum cTnI
195 concentrations above the detection limit already prior to sedation or anaesthesia in
196 comparison to the studies of Saunders et al. (2009), Cilli et al. (2010) and Singletary et
197 al. (2010). Thus far, only Verbiest et al. (2013) used the same cTnI assay as was used
198 in this study. Preanaesthetic cTnI concentrations in their study were above the level of
199 detection in 11 out of 18 dogs (61%). These results suggest that selection of an assay
200 with high analytical sensitivity and a low detection limit is of great importance for
201 reliable interpretation of changes in cTnI concentrations.
202 The cardiovascular effects of medetomidine are dose-related and include bradycardia,
203 decreased cardiac output, vasoconstriction and arrhythmias (Ko et al. 2000).
204 Significantly higher serum cTnI concentration in group M compared to group M+P+S at
205 12 hours after sedation/anaesthesia cannot be attributed to medetomidine, since both
206 groups of dogs were administered the same dose of medetomidine, which was
207 antagonized with atipamezole 35 minutes later. Also, there were no differences between
208 groups in terms of blood pressure and heart rate during sedation/anaesthesia. However,
209 medetomidine sedated dogs breathed room air during sedation while those premedicated
210 with medetomidine and anaesthetized with propofol and sevoflurane breathed oxygen
211 during anaesthesia.
212 Ko et al. (2007) investigated oxygenation status of dogs sedated with the same dose of
213 medetomidine (0.04 mg kg^{-1} IV) as that used in this study and compared dogs breathing
214 room air or oxygen supplemented via a face mask (3 L $minute^{-1}$). One of seven dogs

breathing room air in their study had a hypoxemic episode 10 minutes after medetomidine administration [arterial partial pressure of oxygen (PaO_2) of 59 mmHg], and the rest of the dogs had PaO_2 values between 69 and 93 mmHg. Likewise, Raekallio et al. (2009) observed a slight decrease of PaO_2 five minutes after medetomidine administration (0.02 mg kg^{-1} IV); PaO_2 further decreased after addition of L-methadone (0.1 mg kg^{-1}) to 55 mmHg. The authors of these studies therefore recommended oxygenation of dogs during sedation with medetomidine alone or in combination with opioids.

A limitation of our study is that arterial blood gas analysis was not performed to detect hypoxaemia. Detection of hypoxaemia with pulse oximetry failed in medetomidine sedated dogs because they did not tolerate pulse oximetry probe on the tongue or the monitor reported errors during reading. However, according to the results of the study of Ko et al. (2007), it is reasonable to suspect that dogs which breathed room air during sedation with medetomidine in this study experienced a certain extent of hypoxia during sedation

Dexmedetomidine IV at 0.001 to 0.004 mg kg^{-1} significantly increases coronary vascular resistance and mildly reduces coronary blood flow in enflurane-anaesthetized dogs (Flacke et al. 1993), which indicates that the local vasoconstriction action of medetomidine may restrict oxygen supply to the myocardium leading to potential myocardial hypoxia and release of cTnI. Unbound cytoplasmatic troponin is released within 4 to 6 hours of myocardial injury and reaches a peak concentration at 12 to 24 hours, while release of structural cTnI due to ongoing myocardial injury leads to a second peak 2 to 4 days after injury (Wolfe Barry et al. 2008). In this study, increased serum cTnI concentrations were detected 6 and 12 hours after sedation/anaesthesia in all

239 groups of dogs, but remained increased up to 4 days in medetomidine sedated dogs
240 only. This group of dogs breathed room air during sedation, while the other two groups
241 breathed oxygen during anaesthesia. We presume that the hypoxic insult was severe
242 enough only in medetomidine sedated dogs to also cause a release of structural cTnI,
243 which peaks 2 to 4 days after the myocardial injury (Wolfe Barry et al. 2008).
244 It is interesting that serum cTnI concentration was significantly lower 12 hours after
245 anaesthesia in the M+P+S group in comparison to the P+S group, in which the dogs had
246 significantly lower arterial blood pressure during anaesthesia. Medetomidine given IM
247 or IV at or above 0.03 mg kg^{-1} transiently increases arterial blood pressure (Vainio &
248 Palmu 1989; Cullen & Reynoldson 1993) through stimulation of peripheral postsynaptic
249 α_2-receptors in vascular walls (Savola et al. 1986; Savola 1989). Because of the
250 anaesthetic sparing effect of medetomidine (Vainio 1991; Cullen & Reynoldson 1993;
251 Lagerweij et al. 1993; Sap & Hellebrekers 1993; Hammond & England 1994; Thurmon
252 et al. 1994), a much lower dose of propofol (1.92 ± 0.63 *versus* 6.5 ± 0.76 mg kg^{-1}) was
253 used for induction and a lower dose of sevoflurane (3% versus 4.5%) was used for
254 maintenance of anaesthesia in the M+P+S group compared to the P+S group. Lower
255 doses of propofol and sevoflurane in combination with medetomidine-induced
256 vasoconstriction in the M+P+S group resulted in significantly higher arterial blood
257 pressure and probably better tissue perfusion in this group. However, both anaesthetic
258 protocols caused only mild myocardial injury as evidenced by increased serum cTnI
259 concentration at 6 and 12 hours after anaesthesia but not 4 days later, which corresponds
260 to the release of only unbound cytoplasmatic troponin.
261 Another limitation of this study might be that we did not use a cTnI assay of sufficient
262 sensitivity to quantify and investigate changes in cTnI concentrations. However, the

lower limit of detection of the assay used in this study was very low (0.006 ng mL^{-1}) and is the same as in the high-sensistivity cTnI assay used by Winter et al. (2014) and Winter et al. (2017). Moreover, the results of this study apply only to adult dogs aged up to 10 years and classified as ASA 1 or 2. Younger or older dogs were not recruited as this was clinical study and use of medetomidine at 0.04 mg kg^{-1} IV would not be appropriate due to pronounced medetomidine cardiovascular effects (Vainio & Palmu 1989; Cullen & Reynoldson 1993).

In conclusion, our results indicate that (1) anaesthesia with propofol and sevoflurane with or without premedication with medetomidine causes subclinical myocardial damage as evidenced by short-lived increased serum cTnI concentrations; (2) in dogs anaesthetized with propofol and sevoflurane, serum cTnI concentrations increase less when they are premedicated with medetomidine; (3) only in medetomidine-sedated dogs breathing room air was the hypoxic insult severe enough to cause increased serum cTnI concentration up to 4 days, which corresponds to the release of structural cTnI; (4) even if sedation with medetomidine appears to be a less invasive procedure than general anaesthesia in the eyes of the dog owner, and the dog may recover “normally” when it is breathing room air, supplementation with oxygen during sedation is necessary to prevent hypoxemia and ongoing myocardial injury.

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374 **Figure Legends**

375

376 **Figure 1** Serum cardiac troponin I (cTnI) concentrations before sedation with
377 medetomidine (0.04 mg kg^{-1} IV; n = 20), 6 and 12 hours and 4 days thereafter. The dogs
378 breathed room air. Each line represents data from a single dog.

379

380 **Figure 2** Serum cardiac troponin I (cTnI) concentrations before the dogs (n = 20) were
381 induced to anaesthesia with propofol (6.5 ± 0.76 mg kg^{-1} IV) and anaesthetized with
382 sevoflurane (4.5% vaporizer setting) in oxygen, 6 and 12 hours and 4 days thereafter.
383 Each line represents data from a single dog.

384

385 **Figure 3** Serum cardiac troponin I (cTnI) concentrations before the dogs (n = 26) were
386 premedicated with medetomidine (0.04 mg kg^{-1} IV), induced to anaesthesia with
387 propofol (1.92 ± 0.63 mg kg^{-1}) and anaesthetized with sevoflurane (3% vaporizer
388 setting) in oxygen, 6 and 12 hours and 4 days thereafter. Each line represents data from
389 a single dog.

390

391 **Figure 4** Serum cardiac troponin I (cTnI) concentrations 12 hours after sedation with
392 medetomidine (M group) or anaesthesia with propofol and sevoflurane (P+S group) or
393 with medetomidine, propofol and sevoflurane (M+P+S group); ° represent outliers

Table 2 Mean arterial blood pressure (mmHg) during sedation with medetomidine (group M), anaesthesia with propofol and sevoflurane (group P+S) and anaesthesia with propofol and sevoflurane after medetomidine premedication (group M+P+S)

		M	**P+S**	**M+P+S**
	n	20	20	26
All dogs	MAP (mmHg)	106 (81–117)*	91 (74–105)	105 (87–124)*
cTnI above detection limit before S/A	*n*	9	4	9
	MAP (mmHg)	105 (48–115)*	90 (75–105)	108 (100–122)*
cTnI below detection limit before S/A	*n*	11	16	17
	MAP (mmHg)	108 (81–117)*	92 (74–104)	103 (87–124)*

Data are presented as median (range). *Significantly higher mean arterial blood pressure compared to the P+S group

cTnI, cardiac troponin I; *n*, number of dogs; MAP, mean arterial blood pressure; S/A, sedation/anaesthesia

Table 1 Heart rate during sedation with medetomidine (group M), anaesthesia with propofol and sevoflurane (group P+S) and anaesthesia with propofol and sevoflurane after medetomidine premedication (group M+P+S)

		M	**P+S**	**M+P+S**
All dogs	*n*	20	20	26
	HR (beats minute^{-1})	87 (59–105) *	132 (99–152)	89 (61–98)*
cTnI above detection limit before S/A	*n*	9	4	9
	HR (beats minute^{-1})	89 (59–105)*	132 (99–152)	92 (77–96)*
cTnI below detection limit before S/A	*n*	11	16	17
	HR (beats minute^{-1})	86 (60–105)*	132 (107–145)	84 (61–98)*

Data are presented as median (range). *Significantly lower heart rate compared to the P+S group

cTnI, cardiac troponin I; *n*, number of dogs; HR, heart rate; S/A, sedation/anaesthesia